Declaration

I, Monique BERWAER, declare:

1. That I am a belgian citizen, residing at Ham-sur-Heure-Nalinnes (Belgium).
   That I am a graduate of the University of Liège with the degree of pharmacist.
   That I am an industrial pharmacist since 1989.
   That I am in charge, in the Development Department of UCB PHARMA, S.A., Brussels, of research and development of new galenic formulations, since 1994.
   That I am fully familiar with pharmaceutical technologies, i.e. taste masking technologies (coating, cyclodextins), immediate and slow release formulations (coating, matrix tablets), compression, compaction, extrusion, spheronization, development of emulsions, creams, capsules and syrups.
   That all the experiments mentioned below were carried out by myself or under my supervision and control within UCB PHARMA SA.

2. I note that polyols of low molecular weight and particularly mannitol has proven to be a particularly suitable substance for the improvement of the taste and palatability of oral compositions, like chewable and orodispersible tablets, or dry syrups.

   I further note that, as described in different patent applications, i.e. EP 0 811 374 A1, the use of polyols as mannitol in oral compositions containing active compound of formula I causes instability issues and that the main potential impurity in this

Attachment A

type of formulation is the formation of esters and particularly the monoester of mannitol.

Compatibility studies performed under my direction and control with cetirizine and mannitol have shown the rapid appearance of huge amounts of degradation products. Indeed, if binary mixtures of cetirizine and mannitol are placed at 40°C and 40°C/75% RH, 0.25% and 3.1%, respectively, of ester is detected after only 6 weeks.

This creates a serious stability problem for all compositions containing cetirizine and mannitol.

Compositions having the same excipients in the same amount as example 1 in only one formulation (i.e. no bi-layer) showed a rapid degradation in an open dish 4 weeks stress stability study, compared to example 1 where cetirizine chewable tablets are prepared with 2 formulations.

Composition	Conditions	Mannitol esters (%)
Cetirizine chewable bi-layer tablet (example 1)	40°C/75%RH	0.21
	70°C	0.28
Cetirizine tablet one formulation (i.e. no bi-layer)	40°C/75%RH	0.61
	70°C	2.82

I further note that cetirizine chewable bi-layer tablets as described in example 1 packaged in HDPE bottles or aluminium/aluminium blisters are stable up to at least 24 months in ICH conditions.

On the other hand, compositions having the same excipients as example 2 with the same ratio of mannitol in only one

formulation showed a rapid degradation in stability study at 40°C/75%RH. These compositions were packaged in aluminium/aluminium blisters.

Time	Mannitol ester (%)
2 weeks	0.61
4 weeks	0.98
6 weeks	1.66

The compositions of example 2, where cetirizine dry syrup is formulated in 2 formulations, are very stable in the same conditions as described in table 8 of the application.

The above experiments show that the claimed composition can allow the use of reactive polyols, as mannitol, in oral forms in order to have good taste and palability while avoiding cetirizine degradation and conserving good stability.

It is my professional opinion and belief that the reduction in degradation products of the bilayer tablet of the claimed invention as compared to the single formulation tablet is surprising and unexpected to one skilled in the art. In particular, I note that it is highly unexpected that the bilayer tablet of the claimed invention is stable for at least 24 months in ICH conditions. Thus, it is my professional opinion and belief that claim 39 is not rendered obvious under 35 U.S.C. § 103(a) as unpatentable over Andersen in view of Cherukuri et al. and Reiner et al. as such references fail to teach or suggest the unexpected stability of the claimed composition. Such references fail to teach or suggest that the claimed bilayer tablet formulation has an unexpectedly large reduction in the

degradation products of mannitol esters over single formulations.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date 19 FEB 2003

Monique BERWAER

List of patent applications (Monique Berwaer designated as inventor):

- International patent applications WO 99/28310 entitled "Polymorphic forms"
- International patent application WO 99/01133 entitled "Pharmaceutical composition comprising a cyclodextrin and an active substance"
- International patent application WO 98/41194 entitled "Pharmaceutical composition for controlled release of active substances"
- International patent application WO 03/002098 entitled "Tablet comprising cetirizine and pseudoephedrine"
- International patent application WO 03/059328 entitled "Formulations"
- International patent application International patent application WO 03/057198 entitled "Modified released formulations"
- International patent application WO 04/052367 entitled "Combination of efletirizine and pseudoephedrine
- International patent application WO 08/006528 entitled "pharmaceutical composition comprising levetiracetam."